

Aging, B lymphopoiesis, and patterns of leukemogenesis.

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Authors: Robert A J Signer, Encarnacion Montecino-Rodriguez, Kenneth Dorshkind

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Public Summary:

Aging of tissue specific stem and progenitor cells has been proposed to be the central cause of altered tissue function and diminished regenerative capacity in the elderly. Within the hematopoietic system, the consequences of aging are unbalanced within disparate lineages and their progenitors. In particular, the production of lymphocytes is markedly reduced in the elderly, while the myeloid compartment is thought to be relatively unperturbed. Our research has defined a molecular basis for these dichotomous effects of aging on the hematopoietic system and determined that aging and tumor suppression are mechanistically linked processes. We determined that two genes, p16Ink4a and Arf, are preferentially expressed in lymphoid lineage cells with age. Through both gain and loss of function approaches, we demonstrated that the accumulation of these proteins in lymphoid progenitors underlies their age-related declines in proliferative potential and survival, establishing p16Ink4a and Arf as both biomarkers and effectors of lymphoid lineage aging and senescence. While most studies of immune system aging focus on the effects on functional immunity, this work examined the effects of aging on the development of hematological malignancies, which have disparate manifestations in children and adults. We established that the increased expression of p16Ink4a and Arf, both potent tumor suppressors, conferred upon aged lymphoid progenitors an increased resistance to malignant transformation. These findings provide a molecular basis for the well known clinical phenomenon that lymphoid leukemias, although common in children, do not typically present in adults. These findings may have significant therapeutic implications. First, we demonstrated that inhibiting expression of p16Ink4a and Arf, either by ectopic expression of the polycomb gene Bmi-1 or a specifically targeted shRNA, completely reversed the anti-proliferative effects of aging in lymphoid lineage progenitors. Our data thus identify p16Ink4a and Arf as therapeutic targets whose inhibition may promote tissue regeneration and rejuvenation of the depressed immune system in elderly patients. Second, our findings provide new understanding of the genetics of human cancer. In particular, they suggest why the Ink4a/Arf locus is frequently deleted in lymphoid but not myeloid leukemias. Since p16Ink4a and Arf are not expressed in the myeloid lineage, their deletion would confer no growth benefit to myeloid tumors. However, the deletion of p16Ink4a and Arf in lymphoid lineage cells where they are highly expressed would be greatly advantageous to tumor development. Taken together, these findings establish a genetic basis for the preferential and severe effects of aging on lymphopoiesis and demonstrate that aging and tumor suppression are mechanistically linked processes. The determination that tumor suppressors have concurrent pleiotropic effects in aging and cancer provide significant insight into the development and etiology of human malignancies and therapeutic insights into strategies for promoting regenerative medicine.

Scientific Abstract:

The production of B lymphocytes begins to decline steadily early in adult life and is severely compromised in the elderly. This occurrence has been attributed to intrinsic defects in early hematopoietic progenitors and B cell precursors as well as to microenvironmental changes in aged bone marrow. The aim of this review is to present an overview of B lymphocyte senescence and its underlying causes and to discuss its impact on immune function and leukemogenesis in aged individuals.